IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Roberto FAGNANI et al. Serial No.: 10/054,728 Filed: October 25, 2001 Title: THREE DIMENSIONAL FORMAT BIOCHIPS Group Art Unit: 1639 Examiner: Jeffrey S. Lundgren Confirmation No. 3521 Attorney Docket No.: 71726/6776	Certificate of Transmission/Mailing I hereby certify that this correspondence is being facsimile transmitted to the USPTO, transmitted via the Office electronic filing system, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below: February 21, 2008 — Date /James J. Schumann/ James J. Schumann Registration No. 20,856 Attorney for Applicant(s)

APPEAL BRIEF

Mail Stop: APPEAL BRIEF - PATENT
Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellant submits this Appeal Brief under 37 C.F.R. § 41.37 appealing the final rejection of Claims 1, 3, 5-7, 9, 10, 17, 18, 31-35, 43 and 46 in the Office Action mailed September 24, 2007.

(1) Real Party in Interest

The real party in interest is Biocept, Inc.

(2) Related Appeals and Interferences

No related appeals or interferences are known to Appellant.

(3) Status of Claims

Claims 1, 3, 5-7, 9, 10, 17, 18, 31-35, 43 and 46 were rejected in the September 24, 2007 Final Office Action.

Claims 1, 3, 5-7, 9, 10, 17, 18, 31-35, 43 and 46 are appealed.

Claims 2, 4, 15-16, 19-30, and 37 were canceled.

Claims 8, 11-14, 36, 38-40 and 44-45 are withdrawn from consideration.

(4) Status of Amendments

No amendments have been filed subsequent to the final rejection mailed September 24, 2007.

(5) Summary of Claimed Subject Matter

As pointed out on page 7 of the description, Appellant's selection of an appropriate hydrogel with desired immobilization chemistries created an improved biochip which is effective to selectively sequester target molecules if present in an analyte solution. On the flat surface of the substrate, there are a plurality of discrete individual three-dimensional (3D) cells, which are formed from an isocyanate-functional prepolymer having urethane linkages, which individual 3D cells are at least 20 microns thick. Detection sensitivity is maximized as a result of the three-dimensional character of the microcells accommodating more binding entities than a comparable two-dimensional microspot while the optically clear hydrogel allows for ready detection of target molecules sequestered by the individual 3D cells that form a microarray with the cells at discrete locations on the substrate. The hydrogel affords covalent linkage of the binding entities either directly or through intermediate agents, and the highly aqueous character of a hydrogel is such that the binding entities can assume their native conformations. The preferred hydrogels are a product of a prepolymer of a polyethylene glycol (PEG), polypropylene glycol (PPG) or PEG-PPG of a molecular weight of about 5000 that was reacted with polyisocyanates to form a urethane. This prepolymer, when mixed with the aqueous solution, containing binding entities for example, forms the hydrogel, which is primarily water within a polymer framework, through the creation of urea bonds between some isocyanate groups and amines from other isocyanate groups which have hydrolyzed.

Below are tables providing a summarization of the descriptions set forth above and lists of examples of supporting description within the specification. These representative tables are in fact a "summary", and Appellant does not represent or intend that such a brief presentation, or the accompanying references to the specification, comprises an exhaustive presentation in this regard, as it is in the context of the entire specification and abstract in which the claims are to be viewed and interpreted.

Claim 1

A biochip comprising a solid substrate having a flat top surface	See at least App. Pg. 2, lines 1-2; Pg. 9, lines 3, 4 and 16; and Abstract, lines 1-2.
a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick attached to the flat surface of the substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface, which hydrogel cells are formed from an isocyanate-functional prepolymer with urethane linkages	See at least App. Pg. 7, lines 14-15 and 21-23; Pg. 8, lines 7-16 and 29-33; Pg. 9, line 14; Pg. 10, lines 28-31; Pg. 21, line 6; Pg. 22, lines 30-32; and Abstract, lines 1-4.
a different binding entity immobilized within or upon various of said hydrogel cells by covalent linkage of said binding entity or an intermediate agent with reactive isocyanate groups of said hydrogel, which entity is effective to selectively hybridize to or sequester a target molecule.	See at least App. Pg. 7, line 11; Pg. 9, lines 10-12, 16-20 and 28-29; Pg. 10, lines 26-28; and Abstract, lines 6-7.

Claim 3

A hydrogel comprises polyethylene glycol, polypropylene glycol, or copolymers thereof having a molecular weight of about 5000.	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 23, line 17; and Abstract, lines 3-4.

Claim 18

A hydrogel biochip comprising a solid substrate having a flat top surface	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 23, line 17; and Abstract, lines 3-4.
a plurality of optically clear, individual, three-dimensional hydrogel cells of an isocyanate-functional hydrogel at least about 20 μm thick, comprising polyethylene glycol, polypropylene	See at least App. Pg. 7, lines 14-15 and 21-23; Pg. 8, lines 7-16 and 29-33; Pg. 9, line 14;

glycol, or copolymers thereof having urethane linkages, bound to the top surface of said substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface	Pg. 10, lines 28-31; Pg. 21, line 6; Pg. 22, lines 30-32; and Abstract, lines 1-4.
intermediate agents immobilized within or upon said hydrogel cells by covalent binding to reactive isocyanate groups of said hydrogel; and	See at least App. Pg. 9, line 4; and Pg. 10, lines 26-28.
different protein binding entities bound to said intermediate agents respectively within at least several of said hydrogel cells by interaction therewith in a manner so that said protein binding entities assume their native conformations.	See at least App. Pg. 9, lines 10-12 and 16-20.

Claim 31

A biochip comprising a solid substrate having a flat top surface;	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 23, line 17; and Abstract, lines 3-4.
a plurality of optically clear, individual, three-dimensional hydrogel cells at least about 20 μm thick attached to the surface of the substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface,	See at least App. Pg. 7, lines 14-15 and 21-23; Pg. 8, lines 7-16 and 29-33; Pg. 9, line 14; Pg. 10, lines 28-31; Pg. 21, line 6; Pg. 22, lines 30-32; and Abstract, lines 1-4.
each hydrogel cell being a polymer formed from an isocyanate-functional urethane prepolymer; and	See at least App. Pg. 9, line 24; and Pg. 10, lines 28-31.
different protein binding entities immobilized via linkage to isocyanate groups of said hydrogel within or upon different said hydrogel cells, each protein binding entity being effective to selectively hybridize to or sequester a target molecule.	See at least App. Pg. 9, lines 28-30; and Abstract, lines 4-7.

Claim 32

Hydrogel comprises polyethylene glycol, polypropylene glycol, or copolymers thereof having a molecular weight of at least about 5000 with urethane linkages to polyisocyanates.	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 23, line 17; and Abstract, lines 3-4.

Claim 41

A biochip comprising a solid substrate having a flat top surface	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 23, line 17; and Abstract, lines 3-4.
a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick	See at least App. Pg. 7, lines 14-15 and 21-23; Pg. 8, lines 7-16 and 29-33; Pg. 9, line 14; Pg. 10, lines 28-31; Pg. 21, line 6; Pg. 22, lines 30-32; and Abstract, lines 1-4.
comprising urethane polymers of (i) polyethylene glycol, polypropylene glycol, or copolymers thereof and (ii) polyisocyanates	See at least App. Pg. 10, lines 28-31; and Pg. 13, lines 8-10 and 24-27.
which polymers are isocyanate-functional, and which cells are bound to the flat top surface of said substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface	See at least App. Pg. 13, lines 24-25.
intermediate agents immobilized within or upon said hydrogel cells by covalent linkage to reactive isocyanate groups of said hydrogel; and	See at least App. Pg. 9, line 4; and Pg. 10, lines 26-28.
different protein binding entities bound to said intermediate agents within at least several of said hydrogel cells by interaction therewith in a manner so that said protein binding entities can assume their	See at least App. Pg. 9, lines 10-12 and 16-20.

native conformations.	

Claim 46

A biochip comprising a solid substrate having a flat top surface that is derivatized with groups reactive with isocyanate	See at least App. Pg. 11, lines 15-17; Pg. 13, lines 8-10; Pg. 18, lines 21-28 Pg. 23, line 17; Pg. 35, line 27; and Abstract, lines 3-4.
a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick bound to the flat surface of the substrate at discrete locations which form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface,	See at least App. Pg. 7, lines 14-15 and 21-23; Pg. 8, lines 7-16 and 29-33; Pg. 9, line 14; Pg. 10, lines 28-31; Pg. 21, line 6; Pg. 22, lines 30-32; and Abstract, lines 1-4.
said hydrogel cells being formed from an isocyanate-functional urethane prepolymer wherein up to about 5% of its isocyanate groups are covalently bound to said derivatized groups of said substrate; and	See at least App. Pg. 9, line 24; Pg. 10, lines 28-31; and Pg. 18, lines 28-30.
a different binding entity immobilized within or upon various of said hydrogel cells by covalent linkage of said binding entity or an intermediate agent with reactive isocyanate groups of said prepolymer that forms said hydrogel, said entity being effective to selectively hybridize to or sequester a target molecule.	See at least App. Pg. 9, lines 28-30; and Abstract, lines 4-7.

(6) Grounds of Rejection to be Reviewed

The following issues are presented for review:

Issue 1: Whether claims 1, 3, 5-7, 9, 10, 17, 18, 31-35, 43 and 46 are improper under 35 U.S.C. §112, first paragraph, as having been amended to recite new matter because of the recitation of a "flat top surface"?

Issue 2: Whether claims 1, 3, 5-7, 9, 10, 16, 17, 31-35 and 46 are unpatentable under 35 U.S.C. § 103(a) over Sundberg et al. (U.S. Patent No. 5,624,711) and Braatz et al. (U.S. Patent 5,169,720?

Issue 3: Whether claims 1, 3, 5-7, 9, 10, 16-18, 31-35, 41-43 and 46 are unpatentable under 35 U.S.C. § 103(a) over Wagner et al (U.S. Patent No. 6,406,921) in view of Braatz et al (U.S. Patent No. 5,169,720) and further in view of Sundberg et al (U.S. Patent No. 5,624,711)?

(7) Argument

The following arguments are presented to contest the grounds for rejection presented above.

Issue 1: Whether claims 1, 3, 5-7, 9, 10, 17, 18, 31-35, 43 and 46 are improper under 35 U.S.C. §112, first paragraph, as having been amended to recite new matter because of the recitation of a "flat top surface"?

The original claims variously recited the location of the hydrogel cells on the top surface of the substrate (see for example, claim 18, line 4 and claim 23, line 3). Accordingly, the objection is assumed to be directed to the characterization of the top surface being "flat". It was well known in the art that microarrays or biochips had commonly been formed using simple flat plates, e.g. glass slides (see page 2, lines 1-2). It is set forth in the description that the biochip substrates may be solid flat plates, e.g. glass slides (see page 21, lines 1-2). In Example 1, the droplets are manually spotted onto a glass slide (see page 23, lines 22 and 25). In Example 1A, a glass slide is similarly employed (see page 24, line 13). In Example 2, an amine-coated glass slide is employed (see page 26, line 18). Such slides are also used in Example 3 (see page 27, line 17) and in Example 6 (see page 30, line 9).

It is submitted that it is common knowledge that glass slides have flat top surfaces, and the recitation of this background fact in the claims simply provides a point of reference for the 3D cells which protrude therefrom. In view of the foregoing references throughout the description, it is submitted that this recitation does not constitute the incorporation of new matter, and that the rejection under 35 U.S.C. § 112, first paragraph should be reversed.

Issue 2: Whether claims 1, 3, 5-7, 9, 10, 16, 17, 31-35 and 46 are unpatentable under 35 U.S.C. § 103(a) over Sundberg et al. (U.S. Patent No. 5,624,711) and Braatz et al. (U.S. Patent 5,169,720) ?

Claim 1

U.S. Patent No. 5,624,711 to Sundberg et al. (hereinafter Sundberg) does disclose the creation of an array of ligands on a derivatized flat surface such as silanized glass; however, it is there that the similarity ends between what Sundberg discloses and what Appellant is claiming. Sundberg preferably applies a thin film of a polymer of the types that have been sold for several decades for the stepwise solid phase synthesis of peptides and which are referred to as Merrifield resins, PAM resins, etc (see column 14, lines 24-30). The thin film is uniformly applied as by dipping in a solution (see column 14 lines 19-23), or alternatively, by spin coating (see column 15, lines 31-52). The slides in the Examples are coated by dipping, which creates a uniform layer. The polymer that is coated onto the substrate may be one of these commercially available resins or other materials such as polyacrylamides or carboxymethyldextrans which carry initiation sites for subsequent synthesis of ligands. The resultant product is depicted in Figure 6.

To create the desired array, predefined regions are created. As pointed out in the paragraph on column 10, lines 9-15, the spacing of the synthesis initiation sites is of concern, and there are difficulties in achieving the desired spacing of these sites, including the wetability of the surface and the likelihood of non-specific binding.

Examples 6 and 7 teach the creation of so-called "gel chips" between a sandwich of two glass plates, one of which is then removed, using an *in situ* polymerization process where polyacrylamide gels with synthesis initiation sites are created between such a glass sandwich (see column 25, lines 7-58). However, these are polyacrylamide gels, and it is a uniform gel surface which results. It is not a hydrogel. It is not an array of discrete, individual cells protruding

upward from an otherwise flat top surface, which cells are formed from an isocyanate-functional prepolymer with urethane linkages. Sundberg teaches a uniform gel layer that completely covers the surface, and it is not a hydrogel. Nowhere in the entire Sundberg patent does the word hydrogel appear.

The Examiner is in error in stating that Appellants define hydrogel on page 10, lines 16-18. The appropriate definition is set forth in lines 21-23, which reads as follows:

"Hydrogels are hydrophilic network polymers which are glassy in the dehydrated state and swell in the presence of water to form an elastic gel."

This definition is consistent with the definition found in the internet encyclopedia Wikipedia where hydrogel is defined as a network of polymer chains that are water insoluble and superabsorbent (they can contain over 99% water) natural or synthetic polymers.

This is the character of Appellant's hydrogel: three-dimensional individual cells which are largely water that are attached at discrete locations to the flat surface of the substrate. Sundberg's layer of polyacrylamide gel having initiation sites at which peptides or polynucleotides can be synthesized does not render obvious Appellant's claimed plurality of discrete individual three-dimensional cells which protrude from the otherwise flat top surface that are hydrogels of isocyanate-functional prepolymers with urethane linkages. The chemical composition affords covalent linkage of a binding entity or intermediate agent to the isocyanate groups in the network polymers. These discrete cells of hydrogel that are primarily water when used to assay an aqueous solution of analytes are substantially different than Sundberg's uniform layer of polyacrylamide gel or other such peptide synthesis resin with synthesis initiation sites, where ligands will be subsequently synthesized in predefined regions; such regions are inherently subject to spreading out and to non-specific binding in contrast to Appellant's discrete, individual three-dimensional cells. Such regions in a uniform gel surface simply are not discrete individual three-dimensional cells.

These deficiencies are not overcome by any disclosure in U.S. Patent No. 5,169,720 to Braatz et al. (hereinafter Braatz). To substitute the polymer taught in Braatz for the thin, uniform resin coating taught by Sundberg is simply a combination born in hindsight, as the

purpose and the disclosure of Braatz teaches directly away from the purpose of the Sundberg's thin uniform polymeric coating. Sundberg teaches the *in situ* building of a microarray by synthesis of oligomers at predefinied locations on that surface (see title). To carry out such solid-phase synthesis, they require a polymeric resin having synthesis initiation sites which will serve as the base upon which the solid-phase syntheses can be initiated (see Example 6 beginning at column 24, line 37). Braatz is concerned with the creation of a polyurea-urethane polymer that is protein non-adsorptive, i.e. it is resistant to protein adsorption. Braatz teaches using "a coating in the form of a thin film or a monomolecular or substantially monomolecular layer" (column 9, lines 29-30); it is a uniform film like Sundberg advocates using, but one that is protein non-adsorptive. Such is clearly not a coating that one would consider using as a base for synthesizing peptides or proteins *in situ* to create an array, nor is it one that would be effective.

As pointed out at column 10, lines 12-14 of Braatz, the surface coated with the prepolymer is contacted with water, preferably by immersion in a water bath. Immersion for a very substantial period, e.g. 17 hours (see column 17, lines 9-12) is taught. This step crosslinks the uniform layer of prepolymer by forming urea linkages and eliminates any residual reactive isocyanate groups; thus, it creates a coated substrate that would not be useful in the Sundberg procedure. In fact, it is the antithesis of what Sundberg requires, i.e. a polymeric resin that has highly reactive groups for the initiation of synthesis of oligomers -- because Braatz specifically eliminates any residual isocyanate groups (col. 9, lines 5-7). It is likewise the antithesis of Appellant's claimed product which relies upon the isocyanate groups of the hydrogel network to covalently link either to the binding entities or to intermediate agents.

Although Braatz makes reference to materials in the general class of gels or hydrogels, the last time the word hydrogel is used in the patent is in the paragraph at column 10, lines 25-39, where it is stated that the hydrated polymer coatings of interest are useful for applications where conventional polymers or hydrogels are unacceptable. None of the coatings formed in the five pages of Examples are described as hydrogels. The Braatz surface coating must have sufficient integrity to allow the coated item, e.g. tubing, catheters, labware, filters, etc. to be handled; the entire external surface of an implantable device may be coated (column 11,

lines 58-61). In contrast, Appellant's 3D cells formed from microdroplets are minute spots on a supportive flat surface that consist of an elastic gel that is primarily water.

Thus, in addition to teaching another thin film coating procedure, Braatz contains nothing that would cause one to consider the disclosed polymer as one that would be fairly substitutable for the solid phase synthesis polymers used in Sundberg et al. In view of the foregoing, it is submitted that neither of the references teaches a plurality of individual, discrete three-dimensional hydrogel cells protruding from the top of an otherwise flat top surface which are formed from isocyanate-functional prepolymer with urethane linkages, as both references teach the application of uniform films to the surface of a substrate. Moreover, one would not consider the protein-resistant coating of Braatz as a substitute for the protein synthesis resin used by Sundberg, nor would it be an operative substitute; by its own title, it is protein non-absorptive and would be suitable for neither Sundberg's nor Appellant's purposes.

The rejection of claim 1 based upon the combination of Sundberg in view of Braatz should be reversed.

Claim 3

Claim 3 specifies that the hydrogel is formed from a PEG, PPG or copolymer thereof having a molecular weight of about 5000. Such is the character of the composition used in Example 1 and the other Examples which has been found to provide excellent properties and optical clarity. It is submitted that claim 3 is allowable for the reasons set forth above with respect to claim 1, and further for the reason that, inasmuch as neither of the references teaches the employment of a hydrogel formed from an isocyanate-functional prepolymer with urethane linkages, it should be clear that neither of the references teaches a hydrogel formed from such an isocyanate-functional polymer comprising PEG, PPG, or a copolymer thereof having a molecular weight of about 5000 with urethane linkages. The rejection of claim 3 based upon the combination of Sundberg in view of Braatz should be reversed.

Claims 5-7, 9, 10, 16, 17, 31, 33-35 and 46

It is submitted that the above-listed claims are allowable for the reasons set forth with respect to claim 1.

Claim 32

Claim 32 specifies that the hydrogel is formed from a PEG, PPG or copolymer thereof having a molecular weight of at least about 5000. Such is the character of the preferred class of compositions which were found to provide excellent properties and optical clarity. It is submitted that claim 32 is allowed for the reasons set forth above with respect to claims 1 and 3. Neither of the references teaches the employment of a hydrogel formed from an isocyanate-functional prepolymer with urethane linkages comprising PEG, PPG, or a copolymer thereof having a molecular weight of at least about 5000. The rejection of claim 32 based upon the combination of Sundberg in view of Braatz should be reversed.

Issue 3: Whether claims 1, 3, 5-7, 9, 10, 16-18, 31-35, 41-43 and 46 are unpatentable under 35 U.S.C. § 103(a) over Wagner et al (U.S. Patent No. 6,406,921) in view of Braatz et al (U.S. Patent No. 5,169,720) and further in view of Sundberg et al (U.S. Patent No. 5,624,711) ?

Claim 1

For essentially the same reasons as set forth above with respect to Issue 2, the combination of U.S. Patent No. 6,406,921 to Wagner et al. (hereinafter Wagner) in view of the disclosure of Braatz and further in view of Sundberg, likewise fails to render the claimed invention obvious. Wagner also teaches the application of thin, uniform layers to a substrate. Wagner does teach the creation of a peptide array on a flat silicon wafer or the like, but it is a two-dimensional array that is created using a monomolecular layer as the coating on the substrate. Wagner specifically calls the array a "two-dimensional array" (see column 9, lines 49-50; column 17, lines 2-3; and Examples 1 and 2 in column 21). The coating material is referred to throughout the description as a "monolayer"; for example, the molecules that may create the monolayer are discussed throughout column 19. Evidence of this is also found, in Example 4, where the monolayer is deposited by immersion in a 1 millimolar (mM) solution of DSU in chloroform which is thereafter rinsed with ten volumes of solvent; the layer resulting from immersion in such a dilute concentration would be essentially one molecule or so thick. All this is consistent with Wagner's reference to the array as being a 2D-protein Array (Example 6), or a two-dimensional Array (Example 7) (see subtitles).

The Examiner states that "Wagner et al disclose that the monolayer can be of any thickness on the substrate (see e.g. col. 5, lines 15-35)." This is simply in error. The portion of the description to which the Examiner directs attention is not directed to the monolayer but instead to the use of a coating that may optionally be applied to the surface of the substrate, which may be a reflective metal coating that would facilitate subsequent optical detection

analysis. See also column 8, lines 54 to column 9, line 3. The pertinent description appears at column 5, lines 56-57, where "monolayer" is defined as a single-molecule thick layer of organic molecules on a surface. Regardless of what intermediate agents might be used to connect the binding entities to the molecules that make up the monolayer, it should be clear that this is a two-dimensional array and its thickness would be measured in angstroms not microns. Accordingly, it is submitted that Wagner adds nothing of relevance to the description of Sundberg discussed above.

It is submitted that the Examiner's attempt to combine Braatz with Wagner is no more pertinent as teaching a modification of the Wagner monolayer array than it was of suggesting a modification of the Sundberg array. Wagner does not use a hydrogel. As discussed above, Braatz does not use an isocyanate-functional hydrogel to which protein or other binding entities can be attached by covalent linkage, but it teaches the direct opposite. Braatz teaches away from Appellant's claimed product and synthesizes a composition that is protein non-absorptive. This is the title of the Braatz patent. In the first three lines of the abstract, it is stated that coated devices are disclosed that are characterized by their resistance to nonspecific protein adsorption. As pointed out at column 11, line 64 through column 12, line 38, the Braatz coatings upon labware, such as assay plates, would be such that they can be handled by personnel. Such is not a property of the hydrogel which Appellant discloses and claims; it is an elastic material, the major portion of which would be water. The Examiner, on page 6 of the final rejection, mentions that the Braatz polymers are designed for ease of handling, permitting a wide range of end uses. Appellant's elastic gel microspots are discrete cells which are certainly not intended to be handled.

Although the Examiner includes Sundberg as a part of the second rejection under 35 U.S.C. § 103, the only mention is believed to be found at the bottom of page 6 in the third to last line, "(see Sundberg)". It is uncertain what is meant by this reference, but in any event, the description of Sundberg has been discussed in detail with respect to Issue 2.

In view of the foregoing, the rejection of claim 1 based upon the combination of Wagner in view of Braatz and further in view of Sundberg should be reversed.

Claim 3

As earlier pointed out, claim 3 specifies that the hydrogel is formed from a PEG, PPG or copolymer thereof having a molecular weight of about 5000 which has been found to provide excellent properties and optical clarity. It is submitted that claim 3 is allowable for the reasons set forth above with respect to claim 1, and further for the reason that none of the three references teaches the employment of a hydrogel formed from an isocyanate-functional prepolymer with urethane linkages comprising PEG, PPG, or a copolymer thereof having a molecular weight of about 5000. Wagner discloses the use of (i) alkylsiloxane monolayers ("silanes") on hydroxylated surfaces, (ii) alkyl-thiol/dialkyldisulfide monolayers on noble metals, and (iii) alkyl monolayer formation on oxide-free passivated silicon. The rejection of claim 3 based upon the combination of Wagner in view of Braatz and further in view of Sundberg should be reversed.

Claims 5-7, 9, 10, 16-18, 31, 33-35, 41-43 and 46

It is submitted that the above-listed claims are allowable for the reasons set forth with respect to claim 1.

Claim 32

Claim 32 specifies that the hydrogel is formed from a PEG, PPG or copolymer thereof having a molecular weight of at least about 5000. It is submitted that claim 32 is allowable for the reasons set forth above with respect to claims 1 and 3, and further for the reasons stated in respect of the Issue 2 rejection. The rejection of claim 32 based upon the combination of Wagner in view of Braatz and further in view of Sundberg should be reversed.

(8) Claims Appendix

Provided is a complete listing of all the pending claims involved with this appeal:

1. A biochip comprising:

a) a solid substrate having a flat top surface;

b) a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick attached to the flat surface of the substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface, which hydrogel cells are formed from an isocyanate-functional prepolymer with urethane linkages; and

c) a different binding entity immobilized within or upon various of said hydrogel cells by covalent linkage of said binding entity or an intermediate agent with reactive isocyanate groups of said hydrogel, which entity is effective to selectively hybridize to or sequester a target molecule.

3. The biochip of claim 1 wherein the hydrogel comprises polyethylene glycol, polypropylene glycol, or copolymers thereof having a molecular weight of about 5000.

5. The biochip according to claim 3, wherein the three-dimensional individual hydrogel cells are between about 30 μm and about 100 μm thick.

6. The biochip according to claim 1, wherein said binding entity is directly covalently bound to and within the hydrogel cell through reaction with the isocyanate groups.

7. The biochip of claim 1 wherein about 15% to about 5% of the reactive isocyanates in said prepolymer that forms said cell have reacted to immobilize said binding entities or said intermediate agents.

8. The biochip of claim 1 wherein each said binding entity comprises DNA, RNA or PNA.

9. The biochip of claim 1 wherein each said binding entity comprises an immunoglobin, an enzyme, a receptor, an enzyme inhibitor, an enzyme substrate, or a peptide.

10. The biochip of claim 9 wherein each said binding entity is immobilized within the hydrogel through an interaction with an intermediate agent.

17. The biochip of claim 1 wherein the substrate is optically transparent and has reactive molecules on its top surface to which the hydrogel is covalently bound through some of said isocyanate groups of the polymer.

18. A hydrogel biochip comprising:

a) a solid substrate having a flat top surface;

b) a plurality of optically clear, individual, three-dimensional hydrogel cells of an isocyanate-functional hydrogel at least about 20 μm thick, comprising polyethylene glycol, polypropylene glycol, or copolymers thereof having urethane linkages, bound to the top surface of said substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface;

c) intermediate agents immobilized within or upon said hydrogel cells by covalent binding to reactive isocyanate groups of said hydrogel; and

d) different protein binding entities bound to said intermediate agents respectively within at least several of said hydrogel cells by interaction therewith in a manner so that said protein binding entities assume their native conformations.

31. A biochip comprising:

a) a solid substrate having a flat top surface;

b) a plurality of optically clear, individual, three-dimensional hydrogel cells at least about 20 μm thick attached to the surface of the substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface, each hydrogel cell being a polymer formed from an isocyanate-functional urethane prepolymer; and

c) different protein binding entities immobilized via linkage to isocyanate groups of said hydrogel within or upon different said hydrogel cells, each protein binding entity

being effective to selectively hybridize to or sequester a target molecule.

32. The biochip of claim 31 wherein the hydrogel comprises polyethylene glycol, polypropylene glycol, or copolymers thereof having a molecular weight of at least about 5000 with urethane linkages to polyisocyanates.

33. The biochip of claim 32 wherein each hydrogel cell is between about 20 μm and about 100 μm thick.

34. The biochip of claim 31 wherein each said protein binding entity is directly covalently bound to and within the hydrogel cells through reaction with isocyanate groups of said prepolymer that forms said hydrogel.

35. The biochip of claim 31 wherein with said protein binding entities comprise immunoglobins or aptamers.

41. A biochip comprising:

a) a solid substrate having a flat top surface;

b) a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick comprising urethane polymers of (i) polyethylene glycol, polypropylene glycol, or copolymers thereof and (ii) polyisocyanates, which polymers are isocyanate-functional,

and which cells are bound to the flat top surface of said substrate at discrete locations to form an array of discrete individual three-dimensional cells protruding from said otherwise flat top surface;

c) intermediate agents immobilized within or upon said hydrogel cells by covalent linkage to reactive isocyanate groups of said hydrogel; and

d) different protein binding entities bound to said intermediate agents within at least several of said hydrogel cells by interaction therewith in a manner so that said protein binding entities can assume their native conformations.

42. The biochip of claim 41 wherein said hydrogel is a urethane-based polymer formed from a prepolymer with excess isocyanate groups in an amount of about 0.2 meq/g to about 0.8 meq/g, and wherein said protein binding entities are bound through pairs of intermediate coupling agents.

43. The biochip of claim 41 wherein said intermediate agent is nitrilotriacetic acid.

46. A biochip comprising:

a) a solid substrate having a flat top surface that is derivatized with groups reactive with isocyanate;

b) a plurality of optically clear, individual, three-dimensional hydrogel cells at least 20 μm thick bound to the flat surface of the substrate at discrete locations which form an

array of discrete individual three-dimensional cells protruding from said otherwise flat top surface, said hydrogel cells being formed from an isocyanate-functional urethane prepolymer wherein up to about 5% of its isocyanate groups are covalently bound to said derivatized groups of said substrate; and

c) a different binding entity immobilized within or upon various of said hydrogel cells by covalent linkage of said binding entity or an intermediate agent with reactive isocyanate groups of said prepolymer that forms said hydrogel, said entity being effective to selectively hybridize to or sequester a target molecule.

(9) Evidence Appendix

None

(10) Related Proceedings Appendix

None

CONCLUSION

Appellant submits that the rejections of claims 1, 3, 5-7, 9, 10, 16-18, 31-35, 41-43 and 46 are in error, and submits that these claims do not recite new matter and do define subject matter which is patentable over the Examiner's combination of either two or three references. Appellant respectfully requests reversal of the final rejection and allowance of claims 1, 3, 5-7, 9, 10, 16-18, 31-35, 41-43 and 46.

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Respectfully submitted,

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